Supplemental Material

Supplemental Figure 1. Analysis Scheme.

Supplemental Figure 2. Breakdown of variants identified in *PKD1 & PKD2*.

Supplemental Figure 3. Distribution of all mutations across exons of *PKD1*.

Supplemental Figure 4. Distribution of pathogenic mutations across exons of *PKD1*.

Supplemental Figure 5. Comparison of mutation rate in duplicated (exons 1—33) and non-duplicated (exons 34-46) region of *PKD1*.

Supplemental Figure 6. Coverage of *PKD1* and *PKD2* using whole genome sequencing in BRAVO and gnomAD.

Supplemental Figure 7. Coverage of *PKD1* and *PKD2* using whole exome sequencing in BRAVO and gnomAD.

Supplemental Appendix 1. Cohorts included in gnomAD and BRAVO datasets.

Supplemental Appendix 2. Summary results for *PKD1* and *PKD2* in whole genome and exome sequencing of gnomAD and BRAVO.

Supplemental Appendix 3. Pathological, Likely Pathogenic, and Bioinformatic-predicted PKD1 variants.

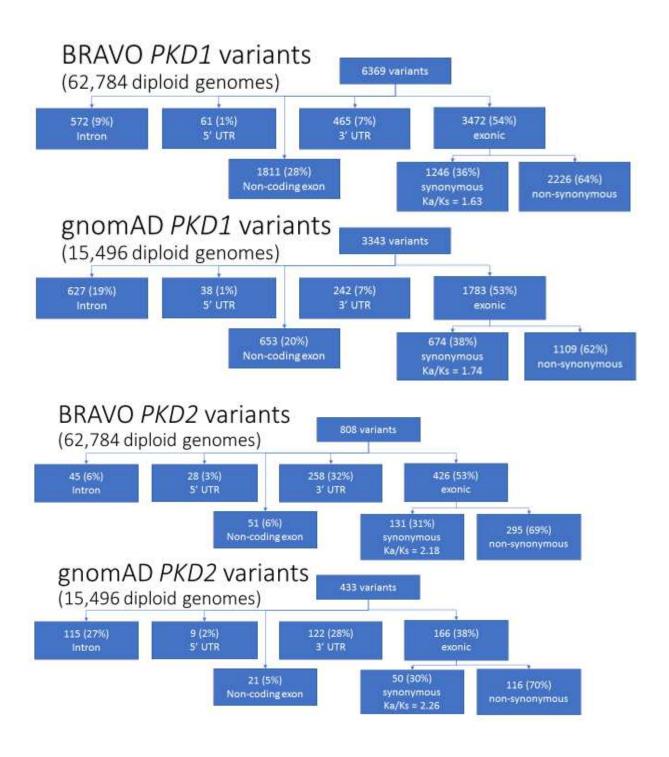
Supplemental Appendix 4. Pathological, Likely Pathogenic, and Bioinformatic-predicted *PKD2* variants.

Supplemental Appendix 5. Likely hypomorphic *PKD1* variants from Mayo PKDB in gnomAD and BRAVO.

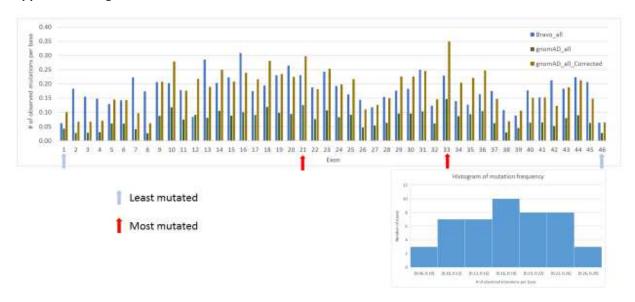
Supplemental Appendix 6. Summary of cystogenic and potential cyst modifying variants.

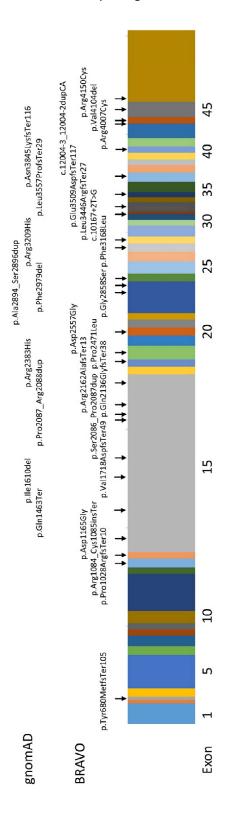
Supplemental Figure 1. Analysis Scheme.

PKD1, PKD2, ALG8, PRKCSH, LRP5, GANAB, SEC63, SEC61B UMOD, REN, MUC1, TSC1, TSC2, HNF1B, VHL, COL4A1, PMM2, COL4A3, COL4A4, COL4A5, PKHD1, DZIP1L gnomAD genome BRAVO gnomAD exome Variant database - Remove all variants MAF > 0.01% in any population - Remove all variants with homozygous observation Remove all intronic & synonymous variants · Determine variant annotation on canonical transcript PKD1: ENST00000262304 PKD2: ENST00000237596 Identify overlap with variants in PKDB + Calculate bioinformatic predictions for missense varints in wANNOVAR Calculate bioinformatic predictions for inframe InDels using VEST4 Filtered variants Pathogenic: protein truncating mutations, including nonsense, frameshift, canonical splice donor or acceptor site mutations, inframe InDels deemed pathogenic in VEST4 (P<0.005), or those listed as "definitely" or "highly likely" pathogenic mutations in PKDB. Likely Pathogenic: likely" pathogenic mutations in PKDB and inframe InDels deemed likely pathogenic in VEST4 (0.05<P<0.005), Bioinformatic: predicted deleterious by more than 12 of 16 bioinformatic prediction algorithms (SIFT, PolyPhen2-HumDiv, PolyPhen2-HumVar, MutationTaster, MutationAssessor, LRT, FATHMM, FATHMM-MKL, PROVEAN, VEST3, MetaSVM, MetaLR, M-CAP, CADD, DANN, GenoCanyon) Overall and ethnic-specific genetic lifetime disease prevalence estimates

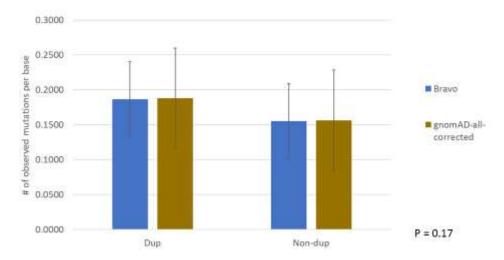


Supplemental Figure 3. Distribution of all observed rare mutations across exons of *PKD1*.

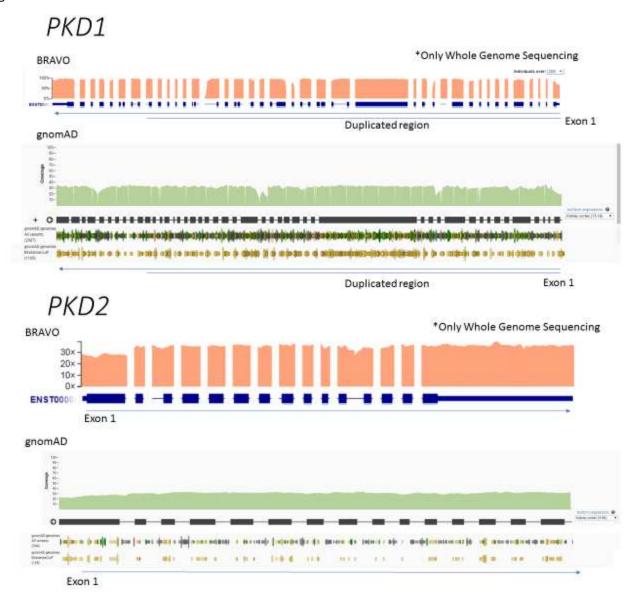




Supplemental Figure 5. Comparison of mutation rate in duplicated (exons 1—33) and non-duplicated (exons 34-46) region of *PKD1*.



Supplemental Figure 6. Coverage of *PKD1* and *PKD2* using whole genome sequencing in BRAVO and gnomAD.



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